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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/071,645	02/06/2002	Bernard Bihain	92.US2.CIP	1680

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EXAMINER	
LOCKARD, JON MCCLELLAND	
ART UNIT	**PAPER NUMBER**
1647	

DATE MAILED: 04/05/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/071,645	BIHAIN ET AL.	
	Examiner	Art Unit	
	Jon M. Lockard	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 January 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *14-23,29,32-34 and 46* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *14-20,22,29,34 and 46* is/are rejected.

7)☐ Claim(s) *21,23,32 and 33* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Sequence Alignment*.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 1/4/2006 has been entered.

Status of Application, Amendments, and/or Claims

2. The Amendment filed 31 August 2005 has been received and entered in full. Claims 14, 20-22, 29, and 34 have been amended, and claims 24-28, 30, 31, and 35-45 have been cancelled. Therefore, claims 14-23, 29, 32-34, and 46 are pending and are the subject of this Office Action.

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Withdrawn Objections and/or Rejections

Claim Rejections

4. The rejections of claims 21, 24-28, 30, 31, and 35-45 under 35 U.S.C. § 112, first paragraph (scope of enablement and written description) as set forth at pg 3-11 of the previous Office Action (mailed 04 May 2005) are withdrawn in view of Applicants amendment of claim 21 and cancellation of claims 24-28, 30, 31, and 35-45 (filed 31 August 2005).

5. The rejection of claim 14 under 35 U.S.C. § 112, second paragraph as set forth at pg 12 of the previous Office Action (mailed 04 May 2005) is withdrawn in view of Applicants amendment of said claim which no longer recites a "variant" and recites specific hybridization conditions (filed 31 August 2005).

6. The rejection of claim 36 under 35 U.S.C. § 112, second paragraph as set forth at pg 11-12 of the previous Office Action (mailed 04 May 2005) is moot in view of Applicants cancellation of said claim (filed 31 August 2005).

7. The rejection of claims 37-40 under 35 U.S.C. § 112, second paragraph as set forth at pg 12 of the previous Office Action (mailed 04 May 2005) is moot in view of Applicants cancellation of said claim (filed 31 August 2005).

8. The rejection of claims 24-28, 30, 31, 35, and 41-45 under 35 U.S.C. § 112, second paragraph for depending from an indefinite claim as set forth at pg 12 of the previous Office Action (mailed 04 May 2005) is moot in view of Applicants cancellation of said claim (filed 31 August 2005).

Maintained and/or New Rejections

Claim Rejections - 35 USC § 112, 1st Paragraph (scope of enablement)

9. Claims 14-20, 22, 29, 34, and 46 remain rejected under 35 U.S.C. 112, first paragraph, for reasons set forth at pg 3-7 in the previous Office Action (mailed 04 May 2005). The specification, while being enabling for (1) a polynucleotide comprising the nucleotide sequence

of SEQ ID NOs:1 and 3; (2) a polynucleotide that encodes a polypeptide comprising the amino acid sequence of SEQ ID NO:2; (3) a polynucleotide that encodes a polypeptide that is at least 95% identical to the amino acid sequence of SEQ ID NO:2 wherein the polypeptide binds to the polypeptide g34872 or a calcium/calmodulin-dependent kinase II (CaM-KII); and (4) a polynucleotide that has at least 95% nucleotide sequence identity with the polynucleotide of SEQ ID NO:1 wherein said polynucleotide encodes a polypeptide that binds to the polypeptide g34872 or CaM-KII, does not reasonably provide enablement for a polynucleotide comprising nucleotide positions 1 to 140; 141 to 460; 460 to 690; or 87 to 346 of SEQ ID NO:1 or nucleotide positions 1 to 3038; 1 to 421; 422 to 557; 2158 to 2218; or 2620 to 3039 of SEQ ID NO:3; polynucleotides which hybridizes under stringent conditions to a polynucleotide comprising nucleotide positions 1 to 140; 141 to 460; 460 to 690; or 87 to 346 of SEQ ID NO:1; polynucleotides that have at least 95% nucleotide sequence identity with the nucleotide sequence of SEQ ID NO:3 wherein said polynucleotide encodes a polypeptide that binds to the polypeptide g34872; polynucleotides that have at least 95% nucleotide sequence identity with the nucleotide sequence of SEQ ID NO:3 wherein said polynucleotide encodes a polypeptide that binds to CaM-KII; polynucleotides that encode a polypeptide comprising an amino acid sequence which is at least 95% identical to the amino acid sequence of SEQ ID NO:2; or a polynucleotide which has at least 95% nucleotide sequence identity with the nucleotide sequence of SEQ ID NO:3. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

10. The specification's disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without undue experimentation. The factors listed below have been considered in the analysis of enablement:

(A) The breadth of the claims;
(B) The nature of the invention;
(C) The state of the prior art;
(D) The level of one of ordinary skill;
(E) The level of predictability in the art;
(F) The amount of direction provided by the inventor;
(G) The existence of working examples; and
(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

11. The claims are drawn to a genus of polynucleotides that are a variant, fragment, analog, or derivative of the polynucleotide sequences set forth in SEQ ID NO:1 and SEQ ID NO:3. While the specification discloses that the protein set forth as SEQ ID NO:2, which is encoded by SEQ ID NOs:1 and 3, binds with the g34872 protein and CaM-KII, the specification fails to describe other sequences or variants that are commensurate in scope with the claims that encode proteins that are capable of binding the g34872 protein or CaM-KII.

12. Applicants argue at pg 6-8 of the response (filed 31 August 2005) that the claims now recite polynucleotides that encode a polypeptide that is at least 95% identical to the amino acid sequence of SEQ ID NO:2, and that the claims and the specification indicate that variants retain the biological activities associated with the PAPAP polypeptide (SEQ ID NO:2), namely, the ability to bind g34872 or CaM-KII. Applicants further argue that the specification discloses two nucleic acid sequences set forth as SEQ ID NO:1 and 3 which encode the polypeptide of SEQ ID NO:2, as well as a method of how to screen for PAPAP polypeptide (SEQ ID NO:2) variants having the biological activity as recited in the claims.

13. The Applicant's arguments have been taken into consideration and are not found persuasive for the following reasons. It is first noted that the pending claims are not limited to polynucleotide sequences that encode polypeptides that share at least 95% sequence identity with the polypeptide of SEQ ID NO:2, nor are the claims limited to polynucleotides that share at least 95% sequence identity to the coding region of the polynucleotide that encodes the polypeptide of SEQ ID NO:2, or that they retain a particular activity, i.e., bind the g34872 polypeptide of CaM-KII. As set forth in the previous Office Action, the state of the art is such that the relationship between the sequence of a protein and its activity is not well understood and unpredictable, and that certain positions in the sequence are critical to the protein's structure/function relationship. The problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. While it is known that many amino acid substitutions are generally possible in any given protein the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited. More importantly, certain positions in the sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. These or other regions may also be critical determinants of antigenicity. These regions can tolerate only relatively conservative substitutions or no substitutions [see Wells (1990) "Additivity of Mutational Effects in Proteins." Biochemistry **29**(37): 8509-8517; Ngo *et al.* (1995) "The Protein Folding Problem and Tertiary Structure Prediction, Chapter 14: Computational Complexity Protein Structure Prediction, and the Levinthal Paradox" pp. 492-495; cited in a previous Office Action]. Although the

specification outlines art-recognized procedures for producing and screening for active variants, this is not adequate guidance as to the nature of active derivatives that may be constructed, but is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. Although Applicant's have asserted an active binding site responsible for the binding of SEQ ID NO:2 to CaM-KII (See pg 6-7 of the response), that may not be sufficient, as the ordinary artisan would immediately recognize that an active or binding site must assume the proper three-dimensional configuration to be active, which conformation is dependent upon surrounding residues; therefore the addition or substitution of non-essential residues can often destroy activity.

14. Additionally, the Examiner has interpreted claim 18 as reading on isolated host cells, as well as host cells in the context of a multicellular, transgenic organism and host cells intended for gene therapy. The specification of the instant application teaches that the PAPAP gene can be used to generate transgenic animals (pg 89-90). The specification also discloses that nucleic acid encoding the PAPAP polypeptide can be used in gene therapy (pg 80-86). However, there are no methods or working examples disclosed in the instant application whereby a multicellular animal with the incorporated PAPAP gene of SEQ ID NO:1 or SEQ ID NO:3 is demonstrated to express the PAPAP peptide of SEQ ID NO:2. Furthermore, the specification does not teach any methods or working examples that indicate a PAPAP nucleic acid is introduced and expressed in a cell for therapeutic purposes. The disclosure in the specification is merely an invitation to the artisan to use the current invention as a starting point for further experimentation since the specification has not taught what the phenotype or use of such a transgenic is, nor any disease or

condition for which gene therapy would be appropriate. (Please note that this issue could be overcome by amending claim 18 to recite, for example, "An isolated host cell...").

15. Due to the large quantity of experimentation necessary to generate the infinite number of derivatives recited in the claims and possibly screen the same for activity, and to express a PAPAP nucleic acid in a cell of an organism for therapy; the lack of direction/guidance presented in the specification regarding which structural features are required in order to provide activity and how to introduce a PAPAP nucleic acid in the cell of an organism to be able produce the encoded protein; the absence of working examples directed to same; the complex nature of the invention; the state of the prior art which establishes the unpredictability of the effects of mutation on protein structure and function; and the breadth of the claims which fail to recite any structural limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Claim Rejections - 35 USC § 112, 1st Paragraph (written description)

16. Claims 14-20, 22, 29, 34, and 46 remain rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the Specification in such a way as to reasonably convey to one skilled in the art that the inventor(s), at the time the application was filed, had possession of the claimed invention for reasons set forth in the previous Office Action (mailed 10 August 2004).

17. The Specification discloses polynucleotides set forth as SEQ ID NOs:1 and 3 that encode the polypeptide of SEQ ID NO:2. However, the claims also recite a polynucleotide comprising

nucleotide positions 1 to 140; 141 to 460; 460 to 690; or 87 to 346 of SEQ ID NO:1 or nucleotide positions 1 to 3038; 1 to 421; 422 to 557; 2158 to 2218; or 2620 to 3039 of SEQ ID NO:3; polynucleotides which hybridizes under stringent conditions to a polynucleotide comprising nucleotide positions 1 to 140; 141 to 460; 460 to 690; or 87 to 346 of SEQ ID NO:1; polynucleotides that have at least 95% nucleotide sequence identity with the nucleotide sequence of SEQ ID NO:3 (genomic) wherein said polynucleotide encodes a polypeptide that binds to the polypeptide g34872; polynucleotides that have at least 95% nucleotide sequence identity with the nucleotide sequence of SEQ ID NO:3 (genomic) wherein said polynucleotide encodes a polypeptide that binds to CaM-KII; or a polynucleotide which has at least 95% nucleotide sequence identity with the nucleotide sequence of SEQ ID NO:3. Thus, the claims are drawn to a genus of DNA molecules.

18. Applicants argue at pg 9-10 of the response (filed 31 August 2005) that the specification specifically describes the chemical structures of a polynucleotide that encodes a polypeptide of SEQ ID NO:2 and a polynucleotide comprising the coding sequence set forth in SEQ ID NOs: 1 or 3 and assert that such a description would constitute sufficiently detailed, relevant identifying characteristics of the claimed subject matter consistent with the holdings set forth in *Enzo*.

19. The Applicant's arguments have been taken into consideration and are not found persuasive for the following reasons. The fact situation in the *Enzo* case is substantively different from that in the instant case; the *Enzo* claims are drawn to a "composition of matter that is specific for *Neisseria gonorrhoeae*", which is then further described by ATCC deposit number and specific sequences that hybridize to such. It is further noted that the hybridization recitation

in *Enzo* is substantively different than that recited in claim 14, as it requires a comparative hybridization that demonstrates specificity of the claimed composition for one strain of *Neisseria* over another. By contrast, claims 14 (parts c and d), 29, and 46 have *no* functional limitations. Furthermore, although Applicant's have asserted an active binding site responsible for the binding of SEQ ID NO:2 to CaM-KII (See pg 6-7 of the response), that may not provide a sufficiently detailed, relevant identification of the characteristics of the claimed subject matter, as the ordinary artisan would immediately recognize that an active or binding site must assume the proper three-dimensional configuration to be active, which conformation is dependent upon surrounding residues; therefore the addition or substitution of non-essential residues can often destroy activity.

20. To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, and any combination thereof. In this case, the only factor present in claims 14(c) and (d), 29, and 46 is a mere chemical property of the DNA in the form of a recitation of comprising a fragment of SEQ ID NOs:1 or 3; hybridizes under stringent conditions to a fragment of SEQ ID NOs:1 or 3; or the recitation of percent identity. The distinguishing characteristics of the claimed genus are not described. The only adequately described species are the nucleic acid sequences represented by SEQ ID NOs:1 and 3 and the polypeptide encoded by SEQ ID NOs:1 and 3 set forth as SEQ ID NO:2; polynucleotides which encode a polypeptide

which have at least 95% sequence identity to the polypeptide of SEQ ID NO:2 and bind g34872 or CaM-KII, and polynucleotides which share at least 95% sequence identity to SEQ ID NO:1 and encode a polypeptide which binds g34872 or CaM-KII. Accordingly, the specification does not provide adequate written description of the claimed genus.

21. *Vas-Cath Inc. v. Mahurkar*, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116).

22. With the exception of the sequences referred to above, the skilled artisan cannot envision the detailed chemical structure of the encompassed polypeptides and DNA molecules, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The nucleic acid itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

23. One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

24. Therefore, only the polynucleotides represented by SEQ ID NOs:1 and 3; polynucleotides which encode polypeptides which have at least 95% sequence identity to the polypeptide of SEQ ID NO:2 and bind g34872 or CaM-KII; and polynucleotides which share at least 95% sequence identity to SEQ ID NO:1 and encode polypeptides which binds g34872 or CaM-KII, but not the full breadth of the claims meet the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Claim Rejections - 35 USC § 102

25. Claims 14-20 are rejected under 35 U.S.C. 102(e) as being clearly anticipated by Kaser et al. (US Pat. No. 6,222,027; priority date May 17, 1999; cited in a previous Office Action).

26. Kaser et al. teach a nucleic acid set forth as SEQ ID NO:1 that comprises nucleotides 2158-2218 of SEQ ID NO:3 of the Instant Application (See attached sequence alignment). This cDNA, in the absence of evidence to the contrary, would also hybridize to a polynucleotide comprising nucleotides 2158-2218 of SEQ ID NO:3 of the Instant Application under stringent conditions. Kaser et al. also teach the nucleic acid further comprising a label (See column 10, lines 49-54), bound to a solid support for use in microarrays (See column 5, lines 59-60), a vector and host cell comprising the nucleic acid (See column 8, lines 29-56), as well as methods of producing the protein and recovering the protein that is produced by the host cell (See column 9, lines 4-12). Thus, the reference of Kaser et al. meets all the limitations of claims 14-20.

Summary

27. No claim is allowed.

Allowable Subject Matter

28. Claims 21, 23, 32, and 33 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Jon M. Lockard, Ph.D.** whose telephone number is **(571) 272-2717**. The examiner can normally be reached on Monday through Friday, 8:00 AM to 6:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Brenda Brumback**, can be reached on **(571) 272-0961**.

The fax number for the organization where this application or proceeding is assigned is **571-273-8300**.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see **http://pair-direct.uspto.gov**. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at **866-217-9197** (toll-free).

Jon M. Lockard, Ph.D.
March 31, 2006

Bridget E. Bunner

BRIDGET BUNNER
PATENT EXAMINER